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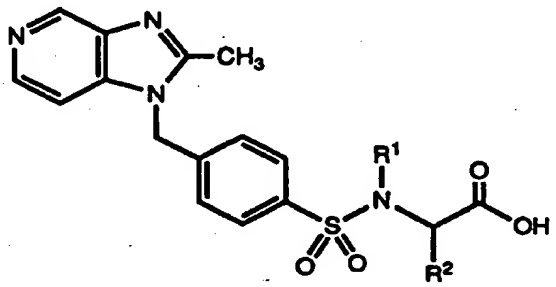
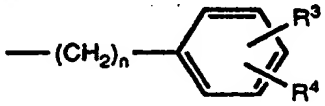
(57) Abstract



(II)



(A)

Compounds of formula (II), wherein R^1 represents hydrogen, -C_1-C_6 alkyl, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, -COC_1-C_6 alkyl, -CO_2C_1-C_6 alkyl, -(COC_1-C_6 alkyl)phenyl, -(CO_2C_1-C_6 alkyl)phenyl, -(C_1-C_6 alkyl)OC_1-C_6 alkyl, -(C_1-C_6 alkyl)SC_1-C_6 alkyl, -(C_1-C_6 alkyl)CO_2C_1-C_6 alkyl, -C_3-C_8 cycloalkyl, -C_4-C_8 cycloalkenyl or a group -D wherein D represents a group (A) wherein n is an integer from 0 to 3, and each of R^3 and R^4 is independently hydrogen, -C_1-C_6 alkyl, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, halogen, -CN, -CO_2H, -CO_2C_1-C_6 alkyl, -$CONH_2$, -$CONHC_1$-C_6 alkyl, -$CONH(C_1$-C_6 alkyl)$_2$, -CHO, -CH_2OH, -CF_3, -OC_1-C_6 alkyl, -SC_1-C_6 alkyl, -SOC_1-C_6 alkyl, -SO_2C_1-C_6 alkyl, -NH_2 or -NHCOMe; R^2 represents hydrogen, halogen, -C_1-C_6 alkyl optionally substituted by one or more halogen atoms, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, -(C_1-C_6 alkyl)CO_2C_1-C_6 alkyl, -(C_1-C_6 alkyl)SC_1-C_6 alkyl, -(C_1-C_6 alkyl)OC_1-C_6 alkyl, -(C_1-C_6 alkyl)$N(C_1$-C_6 alkyl)$_2$, -C_3-C_8 cycloalkyl, -C_4-C_8 cycloalkenyl, -(C_1-C_6 alkyl)C_3-C_8 cycloalkyl, -(C_1-C_6 alkyl)C_4-C_8 cycloalkenyl, -(C_1-C_6 alkyl)OC_3-C_8 cycloalkyl,-(C_1-C_6 alkyl)OC_4-C_8 cycloalkenyl, -(C_1-C_6 alkyl)SC_3-C_8 cycloalkyl, -(C_1-C_6 alkyl)SC_4-C_8 cycloalkenyl, a side chain of a naturally occurring amino acid, a group -D as defined above or a -(C_1-C_6 alkyl)OD group wherein D is as defined above; or a pharmaceutically or veterinarily acceptable salt thereof, are PAF inhibitors.

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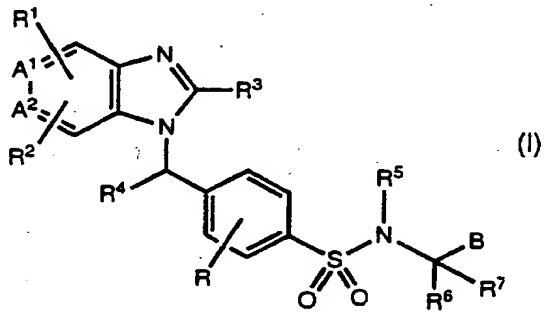
4-(1H-2-METHYLIMIDAZO 4,5-C PYRIDINYLMETHYL)PHENYL SULPHONAMIDE CARBOXYLIC ACID DERIVATIVES AS ANTAGONISTS

This invention relates to the use of certain 4-(1H-2-Methylimidazo[4,5-c]pyridinylmethyl)
phenylsulphonamide derivatives, previously proposed as intermediates in the synthesis of antagonists of platelet activating factor ("PAF"), as active PAF antagonists in their own right, for the preparation of pharmaceutical and veterinary compositions for the management of diseases an conditions mediated by PAF.

Background to the Invention

International Patent Application WO 92/03423 (British Bio-technology Limited) discloses benzimidazole derivatives of formula (I) below, having PAF antagonist activity:



(I)

wherein:

A^1 is =N-, =CH- or =CR^1-;

A^2 is -N=, -CH= or -CR^2=;

provided that, when one of A^1 and A^2 is a nitrogen atom, the other of A^1 and A^2 is other than a nitrogen atom;

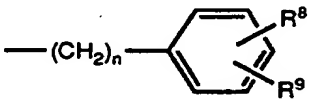
R represents hydrogen, -C_1-C_6 alkyl, -C_2-C_6 alkenyl, halogen or -OC_1-C_6 alkyl;

each of R^1 and R^2 independently represents hydrogen, - C_1-C_6 alkyl, -C_2-C_6 alkenyl, halogen, -CN, -CO_2H, - CO_2C_1-C_6 alkyl, -$CONH_2$, -CHO, -CH_2OH, -CF_3, -OC_1-C_6 alkyl, -SC_1-C_6 alkyl, -SOC_1-C_6 alkyl, -SO_2C_1-C_6 alkyl, -NH_2, -NHCOMe or -NO_2 or R^1 and R^2 together with the carbon atoms to which they are attached form a fused phenyl ring;

R^3 represents hydrogen, -C_1-C_6 alkyl, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, -OC_1-C_6 alkyl, -SC_1-C_6 alkyl, -(C_1-C_6 alkyl)OC_1-C_6 alkyl, -(C_1-C_6 alkyl)SC_1-C_6 alkyl, -CF_3, -(C_1-C_6 alkyl)phenyl, -C_3-C_8 cycloalkyl, -C_4-C_8 cycloalkenyl, -(C_1-C_6 alkyl)C_3-C_8 cycloalkyl, -(C_1-C_6 alkyl)C_4-C_8 cycloalkenyl or thiophenyl;

R^4 represents hydrogen, -C_1-C_6 alkyl, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, -CO_2C_1-C_6 alkyl, -SC_1-C_6 alkyl, -(C_1-C_6 alkyl)SC_1-C_6 alkyl, -(C_1-C_6 alkyl)OC_1-C_6 alkyl, -(C_1-C_6 alkyl)phenyl or thiophenyl;

R^5 represents hydrogen, -C_1-C_6 alkyl, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, -COC_1-C_6 alkyl, -CO_2C_1-C_6 alkyl, -(COC_1-C_6 alkyl)phenyl, -(CO_2C_1-C_6 alkyl)phenyl, -(C_1-C_6 alkyl)OC_1-C_6 alkyl, -(C_1-C_6 alkyl)SC_1-C_6 alkyl, -(C_1-C_6 alkyl)CO_2C_1-C_6 alkyl, -C_3-C_8 cycloalkyl, -C_4-C_8 cycloalkenyl or a group -D wherein D represents a group:



wherein n is an integer from 0 to 3, and each of R^8 and R^9 is independently hydrogen, -C_1-C_6 alkyl, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, halogen, -CN, -CO_2H, -CO_2C_1-C_6 alkyl, -$CONH_2$, - $CONHC_1$-C_6 alkyl, -$CONH(C_1$-C_6 alkyl)$_2$, -CHO, -CH_2OH, -CF_3, - OC_1-C_6 alkyl, -SC_1-C_6 alkyl, -SOC_1-C_6 alkyl, -SO_2C_1-C_6 alkyl, -NH_2 or -NHCOMe;

each of R^6 and R^7 independently represents hydrogen, halogen, -C_1-C_6 alkyl optionally substituted by one or more halogen atoms, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, -(C_1-C_6 alkyl)CO_2C_1-C_6 alkyl, -(C_1-C_6 alkyl)SC_1-C_6 alkyl, -(C_1-C_6 alkyl)OC_1-C_6 alkyl, -(C_1-C_6 alkyl)$N(C_1$-C_6 alkyl)$_2$, -C_3-C_8 cycloalkyl, -C_4-C_8 cycloalkenyl, -(C_1-C_6 alkyl)C_3-C_8 cycloalkyl, -(C_1-C_6 alkyl)C_4-C_8 cycloalkenyl, -(C_1-C_6 alkyl)OC_3-C_8 cycloalkyl, -(C_1-C_6 alkyl)OC_4-C_8 cycloalkenyl, -(C_1-C_6 alkyl)SC_3-C_8 cycloalkyl, -(C_1-C_6 alkyl)SC_4-C_8 cycloalkenyl, a side chain of a naturally occurring amino acid, a group -D as defined above or a -(C_1-C_6 alkyl)OD group wherein D is as defined above;

or R^6 together with R^5 and the atoms to which they are attached form a 5 to 8 membered nitrogen-containing heterocyclic ring;

or R^6 and R^7 together with the carbon atom to which they are attached form a C_3-C_8 cycloalkyl ring;

B represents a) a -ZR^{10} group wherein Z is -C(=O)-, -C(=O)O-, -C(=S)- or -C(=S)O- and R^{10} is -C_1-C_{18} alkyl optionally substituted by one or more halogen atoms, -C_2-C_{18} alkenyl, -C_2-C_{18} alkynyl, -(C_1-C_6 alkyl)OC_1-C_6 alkyl, -(C_1-C_6 alkyl)SC_1-C_6 alkyl, -(C_1-C_6 alkyl)O(C_1-C_6 alkyl)OC_1-C_6 alkyl, -C_3-C_8 cycloalkyl, -C_4-C_8 cycloalkenyl, pyridyl, a group -D as defined above or a -(C_1-C_6 alkyl)OD group wherein D is as defined above;

b) a -$CONR^{11}R^{12}$ group wherein each of R^{11} and R^{12} is independently hydrogen, -C_1-C_{18} alkyl optionally substituted by one or more halogen atoms, -C_2-C_{18} alkenyl, -C_2-C_{18} alkynyl, -C_3-C_8 cycloalkyl, -C_4-C_8 cycloalkenyl, pyridyl, a group -D as defined above or R^{11} and R^{12} together with the nitrogen atom to which they are attached form a 5 to 8 membered nitrogen-containing heterocyclic ring;

In the compounds of formula (I) of WO 92/03423, the carboxylic acid group -CO_2H is not amongst the possibilities specified for substituent B. However, it is stated therein

that compounds of formula (I) wherein B is a group -$CONR^{11}R^{12}$ where R^{11} and R^{12} are as defined in formula (I) may be prepared by treatment of a compound of formula (I) wherein B is a -CO_2R^{10} group wherein R^{10} is a benzyl group with hydrogen in the presence of a noble metal catalyst (eg 10% palladium on charcoal) to give a carboxylic acid which is then treated with an amine of formula $HNR^{11}R^{12}$ in the presence of a coupling reagent (eg 1,3-dicyclohexylcarbodiimide). It is also stated therein that certain compounds of formula (I) wherein B is a -CO_2R^{10} group wherein R^{10} is as defined in formula (I) may be prepared by base catalysed hydrolysis to give a compound of general formula (I) wherein B is a -CO_2H group which is subsequently esterified with an alcohol of general formula HOR^{10} in the presence of a coupling reagent (eg 1,3-dicyclohexylcarbodiimide). Example 77 of WO 92/03423 discloses the carboxylic acid N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridylmethyl)phenylsulphonyl-L-leucine, used as an intermediate in the preparation of its octadecyl ester.

Thus, WO 92/03423 discloses the use of compounds of formula (I) wherein B is a carboxylic acid group -CO_2H as intermediates for the synthesis of PAF antagonists of formula (I) wherein B is an esterified or amidated carboxylic acid group. However, there is no suggestion that the carboxylic acids *per se* have utility as PAF antagonists.

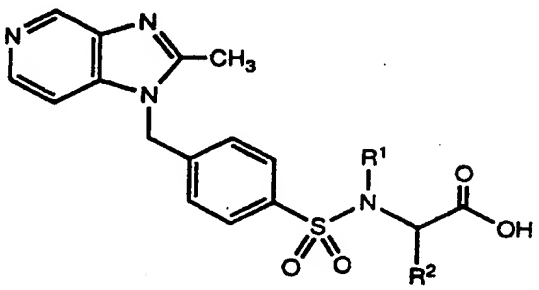
Brief Description of the Invention

The present invention is based on the discovery that carboxylic acids known from WO 92/03423 to be useful as intermediates for the preparation of PAF antagonists disclosed therein, have PAF antagonist activity in their own right. The invention therefore relates to the use of such carboxylic acids in human and veterinary medicine and to pharmaceutical and veterinary compositions comprising them. In connection with the invention, it is of interest that during investigation of the metabolism of N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridylmethyl)phenylsulphonyl-L-leucine ethyl ester, ie the compound of Example 53B of WO 92/03423, following administration of that compound to human beings, it was found that N-methyl-N-4-(1H-2-methylimidazo[4,5-

c]pyridylmethyl)phenylsulphonyl-L-leucine is a primary metabolite (unpublished data).

Description of the Invention

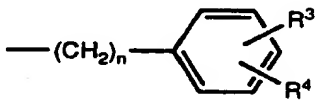
The present invention provides a compound of formula (II):



(II)

wherein

R^1 represents hydrogen, -C_1-C_6 alkyl, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, -COC_1-C_6 alkyl, -CO_2C_1-C_6 alkyl, -(COC_1-C_6 alkyl)phenyl, - (CO_2C_1-C_6 alkyl)phenyl, -(C_1-C_6 alkyl)OC_1-C_6 alkyl, -(C_1-C_6 alkyl)SC_1-C_6 alkyl, -(C_1-C_6 alkyl)CO_2C_1-C_6 alkyl, -C_3-C_8 cycloalkyl, -C_4-C_8 cycloalkenyl or a group -D wherein D represents a group:



wherein n is an integer from 0 to 3, and each of R^3 and R^4 is independently hydrogen, -C_1-C_6 alkyl, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, halogen, -CN, -CO_2H, -CO_2C_1-C_6 alkyl, -$CONH_2$, -$CONHC_1$-C_6 alkyl, -$CONH(C_1$-C_6 alkyl$)_2$, -CHO, -CH_2OH, -CF_3, -OC_1-C_6 alkyl, - SC_1-C_6 alkyl, -SOC_1-C_6 alkyl, -SO_2C_1-C_6 alkyl, -NH_2 or -NHCOMe;

R^2 represents hydrogen, halogen, -C_1-C_6 alkyl optionally substituted by one or

more halogen atoms, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, -(C_1-C_6 alkyl)CO_2C_1-C_6 alkyl, -(C_1-C_6 alkyl)SC_1-C_6 alkyl, -(C_1-C_6 alkyl)OC_1-C_6 alkyl, -(C_1-C_6 alkyl)$N(C_1$-C_6 alkyl)$_2$, -C_3-C_8 cycloalkyl, -C_4-C_8 cycloalkenyl, -(C_1-C_6 alkyl)C_3-C_8 cycloalkyl, - (C_1-C_6 alkyl)C_4-C_8 cycloalkenyl, -(C_1-C_6 alkyl)OC_3-C_8 cycloalkyl, -(C_1-C_6 alkyl)OC_4-C_8 cycloalkenyl, -(C_1-C_6 alkyl)SC_3-C_8 cycloalkyl, -(C_1-C_6 alkyl)SC_4-C_8 cycloalkenyl, a side chain of a naturally occurring amino acid, a group -D as defined above or a -(C_1-C_6 alkyl)OD group wherein D is as defined above;

or a pharmaceutically or veterinarily acceptable salt thereof, for use in human or vererinary medicine.

Hereafter, the term "compound of formula (II)" will be used to refer to a compound as defined in the preceeding paragraph, and is to be understood as referring to the pharmaceutically or veterinarily acceptable salts thereof. Furthermore, the term "pharmaceutical" is to be understood as including both human and veterinary applications.

PAF is released directly from cell membranes and mediates a range of potent and specific effects on target cells resulting in a variety of physiological responses which include hypotension, thrombocytopenia, bronchoconstriction, circulatory shock, and increased vascular permeability (oedema/erythema). It is known that these physiological effects occur in many inflammatory and allergic diseases and PAF has been found to be involved in a number of such disorders including asthma, endotoxin shock, adult respiratory distress syndrome, glomerulonephritis, immune regulation, transplant rejection, gastric ulceration, psoriasis, cerebral, myocardial and renal ischemia. Thus compounds of formula (II) for use in accordance with the invention, by virtue of their ability to antagonise the actions of PAF, may be useful to reduce inflammation and pain, to correct respiratory, cardiovascular, and intravascular alterations or disorders, and to regulate the activation or coagulation of platelets, to correct hypotension during shock, the pathogenesis of immune complex deposition and smooth muscle contractions. In particular, they they have applications in the treatment of inflammatory disorders; such as rheumatoid arthritis, osteoarthritis

and eye inflammation, cardiovascular disorder, thrombocytopenia, asthma, endotoxin shock, adult respiratory distress syndrome, glomerulonephritis, immune regulation, gastric ulceration, transplant rejection, psoriasis, allergic dermatitis, urticaria, multiple sclerosis, cerebral, myocardial and renal ischemia and any other condition in which PAF is implicated.

The invention includes the use of a compound of formula (II) in the preparation of a pharmaceutical composition adapted for oral, topical, rectal or parenteral administration or for inhalation for the management of diseases or conditions mediated by PAF, for example those referred to above. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. Such compositions will include, as is conventional, pharmaceutically acceptable carriers for the active compound, and may contain other conventional pharmaceutical excipients.

Another aspect of the invention is a pharmaceutical composition in dosage unit form, for the management of diseases or conditions mediated by PAF, comprising a compound of formula (II) and one or more pharmaceutically acceptable carriers. Pharmaceutical dosage units are of course known in the art in-general, but are primarily characterised in that the active compound is substantially free of impurities, and present in the dosage unit in a predetermined unit dose amount. In the present case, dosage units include tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups elixirs, phials containing sterile injectable suspensions or solutions of the active ingredient, nebulisers containing solid micronised, or atomisable solutions or suspensions of the active ingredient, Each dosage unit may comprise from about 0.1 mg to about 1g of active ingredient, for example from 10mg to 500 mg, more particularly from 100 to 300mg.

In general, the quantity of active ingredient present in each dosage unit will be chosen to deliver to the patient from about 0.1 mg to abou 0.5 mg to about 7 g per patient per day. For example, for treatment of inflammation, the administration of from about 1.0 mg to about 3.5 g per patient per day may be appropriate. The dosage employed for topical administration will, of course, depend on the size of the

area being treated. For the eyes each dose will be typically in the range from 10 to 100 mg of the drug.

Another aspect of the invention is a method for the management of diseases or conditions mediated by PAF, comprising administering to the patient an effective amount of a compound of formula (II) or a pharmaceutically salt thereof.

As used herein, the term "pharmaceutically acceptable salt" means acid or base addition salts whose anion is generally considered safe for human or animal consumption. Suitable base addition salts include the sodium, potassium, magnesium, lithium, and calcium salts Suitable acid addition salts include the hydrochloride, sulphate, phosphate, acetate, propionate, lactate, maleate, succinate and tartrate salts.

As used herein the term "halogen" or its abbreviation "halo" means fluoro, chloro, bromo or iodo.

As used herein the term "C_1-C_6 alkyl" refers to straight chain or branched chain hydrocarbon groups having from one to six carbon atoms. Illustrative of such alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, neopentyl and hexyl.

As used herein the term "C_2-C_6 alkenyl" refers to straight chain or branched chain hydrocarbon groups having from two to six carbon atoms and having in addition one double bond, of either E or Z stereochemistry where applicable. This term would include for example, vinyl, 1-propenyl, 1- and 2-butenyl and 2-methyl-2-propenyl.

As used herein the term "C_2-C_6 alkynyl" refers to straight chain or branched chain hydrocarbon groups having from two to six carbon atoms and having in addition one triple bond. This term would include for example, ethynyl, 1-propynyl, 1- and 2-butynyl, 2-methyl-2-propynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl and 5-hexynyl.

As used herein, the term "C_1-C_4 perfluoroalkyl" refers to straight chain or branched chain groups having from one to four carbon atoms and substituted by more than one fluorine atom. This term would include for example, trifluoromethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, 3,3,3-trifluoro-n-propyl, sexafluoro-i-propyl, septafluoro-n-propyl, septafluoro-i-propyl, 4,4,4-trifluoro-n-butyl, nonafluoro-n-butyl, nonafluoro-sec-butyl and nonafluoro-i-butyl.

As used herein the term "OC_1-C_6 alkyl" refers to straight chain or branched chain alkoxy groups having from one to six carbon atoms. Illustrative of such alkoxy groups are methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentoxy, neopentoxy and hexoxy.

As used herein the term "SC_1-C_6 alkyl" refers to straight chain or branched chain alkylthio groups having from one to six carbon atoms. Illustrative of such alkyl groups are methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, sec-butylthio, tert-butylthio, pentylthio, neopentylthio and hexylthio.

As used herein, the term "C_3-C_8 cycloalkyl" refers to an alicyclic group having from 3 to 8 carbon atoms. Illustrative of such cycloalkyl groups are cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

As used herein, the term "C_4-C_8 cycloalkenyl" refers to an alicyclic group having from 4 to 8 carbon atoms and having in addition one or more double bonds. Illustrative of such cycloalkenyl groups are cyclopentenyl, cyclohexenyl, cycloheptenyl and cyclooctenyl.

As used herein, the term "side chain of a naturally occurring amino acid" includes the side chains of alanine, arginine, asparagine, aspartic acid, cysteine, cystine, glutamic acid, glycine, histidine, 5-hydroxylysine, 4-hydroxyproline, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine, a-aminoadipic acid, a-amino-n-butyric acid, 3,4-dihydroxyphenylalanine, homoserine, a-methylserine, ornithine, pipecolic acid, and thyroxine. The amino acid side chains may be protected; for example the carboxyl groups of aspartic acid, glutamic acid

and a-aminoadipic acid may be esterified (for example as a C_1-C_6 alkyl ester), the amino groups of lysine, ornithine, 5-hydroxylysine, 4-hydroxyproline may be converted to amides (for example as a COC_1-C_6 alkyl amide) or carbamates (for example as a $C(=O)OC_1$-C_6 alkyl or $C(=O)OCH_2Ph$ carbamate), the hydroxyl groups of 5-hydroxylysine, 4-hydroxyproline, serine, threonine, tyrosine, 3,4-dihydroxyphenylalanine, homoserine, a-methylserine and thyroxine may be converted to ethers (for example a C_1-C_6 alkyl or a (C_1-C_6 alkyl)phenyl ether) or esters (for example a $C(=O)C_1$-C_6 alkyl ester) and the thiol group of cysteine may be converted to thioethers (for example a C_1-C_6 alkyl thioether) or thioesters (for example a $C(=O)C_1$-C_6 alkyl thioester). The stereochemistry at the carbon atom to which the amino acid side chain is attached may be either D or L.

In compounds of formula (II), the presence of several asymmetric carbon atoms gives rise to diastereoisomers, each of which consists of two enantiomers, with the appropriate R or S stereochemistry at each chiral centre. The invention is understood to include the use of all such diastereoisomers, their optically active enantiomers and mixtures thereof.

Although this application relates only to compounds of formula (II) in which the substituents R^1, and R^2 are the only variables it is understood that the introduction of further substituents on the 2-methylimidazo[4,5-c]pyridinyl group, the benzylic carbon atom and/or the 1,4-disubstituted phenyl ring will lead to compounds that retain PAF antagonist activity.

Preferred compounds for use according to the invention include those in which, independently or in any compatible combination:

R^1 represents a hydrogen atom, a -C_1-C_6 alkyl (for example methyl, ethyl or propyl) group, a -C_2-C_6 alkenyl (for example allyl) group or a group -D;

R^2 represents a hydrogen atom, a -C_1-C_6 alkyl (for example ethyl, n-butyl, t-butyl or neopentyl) group, a -C_2-C_6 alkenyl (for example allyl) group, a -(C_1-C_6 alkyl)C_3-C_8 cycloalkyl (for example cyclopropylmethyl, cyclopentylmethyl or

cyclohexylmethyl) group, a side chain of a naturally occurring amino acid (for example the side chain of leucine, isoleucine, phenylalanine, valine, tryptophan, methionine or tyrosine) or a group D;

in the group D, R^3 represents a hydrogen atom, a $-C_1-C_6$ alkyl (for example methyl) group, a halogen (for example fluorine, chlorine or bromine) atom, a $-CF_3$ group or a $-OC_1-C_6$ alkyl (for example methoxy) group;

in the group D, R^4 represents a hydrogen atom or a $-OC_1-C_6$ alkyl (for example methoxy) group;

Examples of compounds of formula (II) for use in accordance with the present invention are:

N-4-(1H-2-Methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl -L-leucine;
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-D-leucine;
N-Ethyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucine;
N-Allyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucine;
N-Propyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucine;
N-Benzyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucine;
N-4-Methoxybenzyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmeth yl) -phenylsulphonyl-L-leucine;
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-isoleucine;
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-phenylalanine;
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-valine;

N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-tryptophan,
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-methionine;
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-O-methyl-L-tyrosine;
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)pheny lsulphonyl-L-norleucine;
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-phenylglycine;
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-t-butylglycine;
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-D,L-ethylglycine;
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-D,L-allylglycine;
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-t-butylalanine;
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-cyclopropylalanine;
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsu lphonyl-L-cyclopentylalanine;
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-cyclohexylalanine;

and their pharmaceutically acceptable salts.

A compound of formula (II) which is at present particularly preferred for use in accordance with the present invention is N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridylmethyl)phenylsulphonyl-L-leucine and its pharmaceutically acceptable salts.

Compounds of the invention may be prepared in accordance with the disclosures of WO 92/03423 by hydrolysis of corresponding esters (prepared as disclosed in WO 92/03423, or by catalytic hydrogenation of the corresponding benzyl esters, or by

other methods known in the art.

It has been found that the compounds of general formula (II) exhibit *in vitro* and *in vivo* antagonistic activities with respect to PAF. Compounds of general formula (II) inhibit PAF-induced functions in both the cellular and tissue levels by changing the PAF binding to its specific receptor site. The ability of compounds of general formula (II) to inhibit the binding of PAF to its specific receptor binding site on human platelet plasma membranes was measured according to Pharmacological Example 1. The ability of compounds of general formula (II) to reverse the hypotension caused by an infusion of PAF in rats was measured according to Pharmacology Example 2.

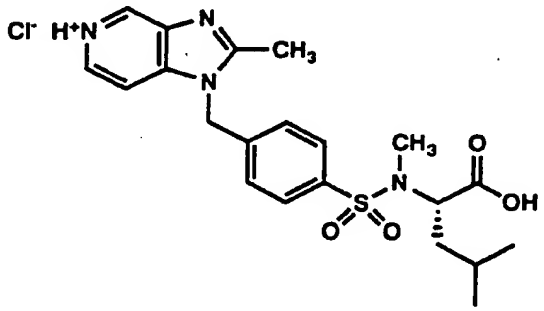
The following abbreviations have been used in the Examples:-

DCM - Dichloromethane
DIPE - Diisopropylether
DMF - N,N-Dimethylformamide
HPLC - High performance liquid chromatography
NBS - N-Bromosuccinimide
TDA-1 - Tris(2-(2-methoxyethoxy)ethyl)amine
THF - Tetrahydrofuran
TLC - Thin layer chromatography

Column chromatography was performed with "flash" grade silica gel. Unless otherwise stated anhydrous magnesium sulphate or anhydrous sodium sulphate was used for drying organic solutions. Unless otherwise stated ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AC-250 spectrometer at 250 MHz and 62.9 MHz respectively using $CDCl_3$ as a solvent and internal reference and are reported as δ ppm from TMS.

Example 1

N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucine hydrochloride



(a) 4-Bromomethylphenylsulphonylchloride

To a solution of p-toluenesulphonyl chloride (50 g, 0.26 mol) in benzene (150 ml) and NBS (46.7 g, 0.26 mol) heated at reflux was added 2,2'-azobis(2-methylpropionitrile) (100 mg). The mixture was heated at reflux for 12 h and allowed to cool to room temperature. The white precipitate of succinimide that formed was separated and discarded. The filtrate was taken up in DCM (200 ml) and washed with water (3 x 100 ml) followed by brine (100 ml) and dried. Filtration, concentration and subsequent crystallisation (from DIPE) gave in two crops 4-bromomethylphenylsulphonylchloride (46.3 g, 66%) as a white crystalline solid.

m.p. 75-76°C

δ_H 8.02 (2H, d, J 8.5 Hz), 7.64 (2H, d, J 8.5 Hz), 4.52 (2H, s).

(b) N-4-Bromomethylphenylsulphonyl-L-leucine ethyl ester

L-leucine ethyl ester hydrochloride (75.0 g. 0.403 mol) was suspended in THF (300 ml) at 0°C, and triethylamine (67 ml, 0.484 mol) added slowly. After stirring for 15 mins a solution of 4-bromomethylphenylsulphonyl chloride (108.4 g, 0.403 mol) in THF (100 ml) was added *via* cannular. The reaction mixture was allowed to stir overnight at ambient temperature. The solvent was removed under low pressure and the organics were extracted into ethyl acetate (200 ml) and washed with water (100 ml) and brine (100 ml). The organic portion was dried, filtered and the solvent evaporated under low pressure. The product was recrystallised from DIPE (500 ml)

to give N-4-bromomethylphenylsulphonyl-L-leucine ethyl ester (134.0 g, 85%) as a white crystalline solid.

δ_H 7.84 (2H, d, J 8.3 Hz), 7.52 (2H, d, J 8.3 Hz), 5.06 (1H, d, J 10.1 Hz), 4.61 (2H, s), 3.97-3.82 (3H, m), 1.85-1.79 (1H, m), 1.49 (2H, dd, J 7.3, 7.2 Hz), 1.08 (3H, t, J 7.1 Hz), 0.92 (3H, d, J 6.7 Hz), 0.91 (3H, d, J 6.5 Hz).

(c) N-4-Azidomethylphenylsulphonyl-L-leucine ethyl ester

A solution of sodium azide (75.0 g, 1.054 mol) in water (150 ml) was added to a solution of the N-4-bromomethylphenylsulphonyl-L-leucine ethyl ester (89.0 g, 0.221 mol) in dichloromethane (150 ml). Benzyltriethylammonium chloride (10 g, 0.044 mol) was added and the heterogenous reaction mixture stirred vigorously for 60 h. The organic portion was separated, washed thoroughly with water, dried, filtered and concentrated to a golden oil, which crystallised on standing. The resulting white solid was freeze dried overnight to yield N-4-azidomethylphenylsulphonyl-L-leucine ethyl ester (78.2 g, 97%).

m.p. 75-77°C

Analysis calculated for $C_{15}H_{22}N_4O_4S$
Requires C 50.83 H 6.26 N 15.81
Found C 50.80 H 6.28 N 15.82

i.r. (DCM) 2930, 2100, 1730, 1335, 1150 cm^{-1}

$[a]_D^{25}$ -16.4° (c 2.0, DCM)

δ_H 7.86 (2H, d, J 8.4 Hz), 7.45 (2H, d, J 8.6 Hz), 5.13, (1H, d, J 10.0 Hz), 4.43 (2H, s), 3.98-3.84 (3H, m), 1.83-1.75 (1H, m), 1.49 (2H, dd, J 7.7, 6.7 Hz), 1.09 (3H, t, J 7.1 Hz), 0.91 (3H, d, J 6.7 Hz), 0.89 (3H, d, J 6.5 Hz).

(d) N-Methyl-N-4-azidomethylphenylsulphonyl-L-leucine ethyl ester

A 60% dispersion of sodium hydride in mineral oil (9.68 g, 0.242 mol) was added in portions to a solution of N-4-azidomethylphenylsulphonyl-L-leucine ethyl ester (78.0 g, 0.220 mol) in THF (200 ml) at 0°C. After stirring for 20 mins iodomethane (28 ml, 0.44 mol) was added slowly, and the reaction allowed to warm to ambient

temperature overnight. Saturated ammonium chloride solution (ca. 15 ml) was added and the THF removed under reduced pressure. The resulting residue was taken up in dichloromethane, washed with saturated hydrogen carbonate solution then water, dried, filtered and concentrated to give N-methyl-N-4-azidomethylphenylsulphonyl-L-leucine ethyl ester as an orange oil (76.0 g, 94%).

Analysis calculated for $C_{16}H_{24}N_4O_4S$
Requires C 52.16 H 6.57 N 15.21
FoundC 52.20 H 6.54 N 15.12

i.r. (DCM) 2100, 1735, 1340, 1160 cm^{-1}

$[a]_D^{20}$ -15.3° (c 2.2, DCM)

δ_H 7.83 (2H, dd, J 8.2, 1.6 Hz), 7.45 (2H, br d, J 8.3 Hz), 4.71-4.65 (1H, m), 4.44 (2H, s), 3.96-3.86 (2H, m), 2.86 (3H, s), 1.67-1.58 (3H, m), 1.09 (3H, t, J 7.1 Hz), 0.99 (3H, d, J 5.0 Hz), 0.97 (3H, d, J 6.1 Hz).

(e) N-Methyl-N-4-aminomethylphenylsulphonyl-L-leucine ethyl ester

Triphenylphosphine (101.80 g, 0.388 mol) was added to a solution of N-methyl-N-4-azidomethylphenylsulphonyl-L-leucine ethyl ester (71.5 g, 0.194 mol) in a mixture of THF and water (4:1, 200 ml), and the reaction mixture stirred overnight at ambient temperature. The THF was removed under reduced pressure, and the product extracted with ethyl acetate, dried, filtered and concentrated to an orange oil. This was purified by chromatography (silica: gradient elution; 1:2 ethyl acetate/hexane; ethyl acetate; 10% methanol in ethyl acetate) to give N-methyl-N-4-aminomethylphenylsulphonyl-L-leucine ethyl ester (38 g, 58%) as a yellow oil.

δ_H 7.76 (2H, dd, J 8.5, 1.7 Hz), 7.45 (2H, d, J 8.3 Hz), 4.71-4.65 (1H, m), 3.95 (2H, s), 3.95-3.85 (2H, m), 2.83 (3H, s), 1.95 (2H, br s), 1.68-1.57 (3H, m), 1.06 (3H, t, J 7.1 Hz), 0.97 (3H, d, J 5.4 Hz), 0.95 (3H, d, J 5.9 Hz).

(f) N-Methyl-N-4-(N'-3-nitropyridin-4-yl)aminomethylphenylsulphonyl-L-leucine ethyl ester

4-Chloro-3-nitropyridine (6.0 g, 38 mmol) was added to a stirred solution of N-methyl-

N-4-aminomethylphenylsulphonyl-L-leucine ethyl ester (13.0 g, 38 mmol) and triethylamine (5.3 ml, 38 mmol) in chloroform (150 ml) at ambient temperature. The reaction mixture was stirred for 60 h, then washed with water, dried, filtered and the solvent removed under reduced pressure to leave a brown oil. This was purified by chromatography over silica (gradient elution; 33% ethyl acetate in hexane; ethyl acetate) to give N-methyl-N-4-(N'-3-nitropyridin-4-yl)aminomethyl-phenylsulphonyl-L-leucine ethyl ester (10.9 g, 62%) as a yellow amorphous solid.

m.p. 71-75°C

i.r. (DCM) 3390, 1730, 1510, 1330 cm^{-1}

$[a]_D^{25}$ -13.8° (c 2.0, DCM)

d_H 9.00 (1H, s) 8.55 (1H, t, J 5.9 Hz), 8.04 (1H, d, J 6.1 Hz), 7.60 (2H, d, J 8.3 Hz), 7.32 (2H, d, J 8.3 Hz), 6.50 (1H, d, J 6.2 Hz), 4.57 (2H, d, J 5.9 Hz), 4.50-4.44 (1H, m), 3.75-3.62 (2H, m), 2.69 (3H, s), 1.45 (3H, br d), 0.86 (3H, t, J 7.1 Hz) 0.77 (6H, d, J 5.9 Hz).

(g) N-Methyl-N-4-(N'-3-aminopyridin-4-yl)aminomethylphenylsulphonyl-L-leucine ethyl ester

A solution of N-methyl-N-4-(N'-3-nitropyridin-4-yl)aminomethylphenylsulphonyl-L-leucine ethyl ester (10.9 g, 0.023 mol) in ethanol (40 ml) was hydrogenated at 100 p.s.i. overnight in the presence of 10% palladium on charcoal (1.0 g). The catalyst was removed by filtration through GF/F filter paper, and the filtrate evaporated under reduced pressure to give N-methyl-N-4-(N'-3-aminopyridin-4-yl)aminomethylphenylsulphonyl- L-leucine ethyl ester (8.90 g, 87%) as a brown foam.

δ_H 7.86 (1H, s) 7.83 (1H, d, J 5.5 Hz), 7.73 (2H, d, J 8.3 Hz), 7.41 (2H, d, J 8.3 Hz), 6.29 (1H, d, J 5.4 Hz), 5.09-4.97 (1H, m), 4.67-4.61 (1H, m), 4.44 (2H, d, J 5.6 Hz), 3.90-3.81 (2H, m), 2.84 (3H, s), 1.62-1.57 (5H, m), 1.04 (3H, t, J 7.1 Hz), 0.96 (3H, d, J 6.0 Hz), 0.95 (3H, d, J 6.1 Hz).

(h) N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucine ethyl ester

N-Methyl-N-4-(N'-3-aminopyridin-4-yl)aminomethylphenylsulphonyl- L-leucine ethyl ester (8.90 g, 20.5 mmol) was refluxed overnight in acetic anhydride (90 ml). The reaction mixture was allowed to cool, then methanol added cautiously until effervescence ceased. The volatiles were removed under reduced pressure and the residue partitioned between saturated sodium hydrogen carbonate solution and ethyl acetate. The organic portion was washed with saturated sodium hydrogen carbonate (x3), and water, dried, filtered and concentrated to a brown oil. This was passed down a pad of silica (3% methanol in DCM) to remove baseline material, and the product further purified by medium pressure liquid chromatography (silica gel: 3% methanol in DCM plus trace of triethylamine) to give a pale yellow oil (5.12 g, 55%), which solidified slowly on standing. Recrystallisation from ethyl acetate/DIPE gave N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucine ethyl ester as a white crystalline solid.

m.p. 105°C

Analysis calculated for $C_{23}H_{30}N_4O_4S$
Requires C 60.24 H 6.60 N 12.22
FoundC 60.21 H 6.59 N 12.08

i.r. (KBr) 2960, 1730, 1330, 1150 cm^{-1}

$[a]_D^{20}$ -6.7° (c 2.0, CDCl3)

δ_H 9.03 (1H, s), 8.37 (1H, d, J 5.5 Hz), 7.76 (2H, d, J 8.4 Hz), 7.18-7.11 (3H, m), 5.39 (2H, s), 4.65-4.59 (1H, m), 3.83 (2H, q, J 7.1 Hz), 2.82, (3H, s), 2.59 (3H, s), 1.69-1.55 (3H, m), 1.02.(3H, t, J 7.1 Hz), 0.97 (3H, d, J 6.1 Hz), 0.95 (3H, d, J 6.2 Hz).

(i) N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridylmethyl)phenylsulphonyl-L-leucine hydrochloride

A solution of N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridylmethyl)-phenylsulphonyl-L-leucine ethyl ester (6.00 g, 13 mmol) in 8M hydrochloric acid (100 ml) was refluxed for 3 hours. The reaction mixture was concentrated to an orange gum which was taken up in ethyl acetate and evaporated to dryness, to give N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridylmethyl)phenyl-sulphonyl-L-leucine

(5.30 g, 87%) as a pale yellow solid.

i.r. (KBr) 1725, 1338, 1157 cm^{-1}

δ_H (d^6 DMSO) 9.42 (1H, s), 8.67 (1H, d, J 6.6 Hz), 8.28 (1H, d, J 6.6 Hz), 7.75 (2H, d, J 8.3 Hz), 7.40 (2H, d, J 8.3 Hz), 5,87 (2H, s), 4.39 (1H, dd, J 9.1), 5.5 Hz), 2.75 (3H, S), 2.64 (3H, s), 2.50-1.40 (3H, m), 0.86 (3H, d, J 6.2 Hz), 0.82 (3H, d, J 6.0 Hz).

Example 2

N-Methyl-N-4-(1H-2-Methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucine

The title compound was prepared from N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucine ethyl ester by base hydrolysis according to Example 77 of WO 92/03423.

Example 3

N-4-(1H-2-Methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucine

The title compound was prepared from N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucine ethyl ester by base hydrolysis in an analogous manner to that for preparation of the compound of Example 2 above. Characterising data:

^{1}H-NMR; δ (d^4-MeOH), 8.64 (1H, s), 8.32 (1H, d, J=5.7Hz), 7.78 (2H, d, J=8.4Hz), 7.68 (1H, d, J=5.7Hz), 7.29 (2H, d, J=8.4Hz), 5.65 (2H, s), 3.73 (1H, t, J=7.6Hz), 2.63 (3H, s), 1.70-1.59 (1H, m), 1.42 (2H, m), 0.81 (3H, d, J=6.6Hz), 0.72 (3H, d, J=6.6Hz).

^{13}C-NMR; δ (d^4-MeOH), 175.6, 160.5, 150.1, 142.3, 141.2, 140.4, 132.4, 129.3, 129.0, 128.6, 128.4, 115.3, 55.6, 48.5, 43.1, 25.5, 23.2, 21.6, 21.4, 14.0.

Example 4

N-Allyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucine

The title compound was prepared from N-allyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucine ethyl ester by base hydrolysis in an analogous manner to that for preparation of the compound of Example 2 above.
Characterising data:

^{1}H-NMR; δ ($CDCl_3$), 8.77 (1H, s), 8.10 (1H, bs), 8.02 (1H, s), 7.86 (2H, d, J=8.3Hz), 7.16 (2H, d, J=8.0Hz), 6.20-5.92(1H, m), 5.50 (2H, d, J=5.6Hz), 5.18 (1H, d, J=17.1Hz), 5.11 (1H, d, J=10.2Hz), 4.72-4.66 (1H, m), 4.14-3.95 (1H, m), 3.84-3.74 (1H, m), 2.55 (3H, s), 1.83-1.69 (3H, m), 1.04 (3H, d), 0.93 (3H, d, J=6.6Hz).

^{13}C-NMR; δ ($CDCl_3$), 174.3, 155.4, 141.6, 140.3, 139.1, 138.8, 138.6, 136.4, 136.3, 128.8, 126.3, 116.7, 105.7, 59.3, 48.5, 47.3, 39.3, 24.1, 22.8, 20.9, 13.9.

Examples 5-24

The compounds of Examples 5-24 are prepared as their hydrochloride acid addition salts by the method of Example 1 employing the appropriate amino acid derivative *in lieu* of L-leucine ethyl ester hydrochloride in Step (b) and for certain compounds missing out the methylation Step (d) or employing a different alkyl halide *in lieu* of methyl iodide in Step (d).

5. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-D-leucine

6. N-Ethyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucine

7. N-Propyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucine

8. N-Benzyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucine

9. N-4-Methoxybenzyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl) phenylsulphonyl-L-leucine

10. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-isoleucine

11. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-phenylalanine

12. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-valine

13. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-tryptophanol

14. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-methionine

15. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-O-methyl-L-tyrosine

16. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-norleucine

17. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-phenylglycine

18. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-t-butylglycine

19. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-D,L-ethylglycine

20. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-D,L-allylglycine

21. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-t-

butylalanine

22. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-cyclopropylalanine

23. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-cyclopentylalanine

24. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-cyclohexylalanine

PHARMACOLOGY EXAMPLE 1

The inhibition of [^{3}H]-PAF binding to human platelet plasma membrane by compounds of general formula I was determined by isotopic labelling and filtration techniques. Platelet concentrates were obtained from a hospital blood bank. These platelet concentrates (500-2500 ml.) were centrifuged at 800 rpm for 10 minutes in a SORVALL RC3B centrifuge to remove the red blood cells present. (The word SORVALL is a trade mark.) The supernatant was subsequently centrifuged at 3,000 rpm in a SORVALL RC3B centrifuge to pellet the platelets present. The platelet rich pellets were resuspended in a minimum volume of buffer (150 mM NaCl, 10 mM Tris, 2 mM EDTA, pH 7.5) and layered onto Ficoll-Paque gradients, 9 ml platelet concentrate to 2 ml Ficoll, and centrifuged at 1,900 rpm for 15 minutes in a SORVALL RT6000 centrifuge. This step removes the residual red blood cells and other nonspecific material such as lymphocytes from the preparation. The platelets which form a band between the plasma and the Ficoll were removed, resuspended in the above buffer and centrifuged at 3,000 rpm for 10 minutes in a SORVALL RT6000 centrifuge. The pelleted platelets were resuspended in buffer (10 mM Tris, 5mM $MgCl_2$, 2 mM EDTA, pH 7.0), snap freezed in liquid N_2 and allowed to thaw slowly at room temperature in order to lyse the platelets. The latter step was repeated at least 3 times to ensure proper lysis. The lysed platelets were centrifuged at 3,000 rpm for 10 minutes in a SORVALL RT6000 centrifuge and resuspended in buffer. The latter step was repeated twice in order to remove any cytoplasmic proteins which may hydrolyse the platelet activating factor (PAF) receptor. The prepared platelet

membranes may be stored at -70°C. After thawing the prepared membranes were centrifuged in a SORVALL RT6000 at 3,000 rpm for 10 minutes and resuspended in assay buffer.

The assay was conducted by preparing a series of Tris-buffered solutions of the selected antagonist of predetermined concentrations. Each of these solutions contained [^{3}H]-PAF (0.5 nM; 1-*O*-[^{3}H]octadecyl-2-acetyl-*sn*-glycero-3-phosphoryl choline with a specific activity of 132 Ci/mmol), unlabelled PAF (1000 nM), a known amount of the test antagonist, and a sufficient amount of Tris-buffer solution (10mM Tris, 5mM $MgCl_2$, pH 7.0, 0.25% BSA) to make the final volume 1ml. Incubation was initiated by the addition of 100 µg of the isolated membrane fraction to each of the above solutions at 0°C. Two control samples, one (C1) which contained all the ingredients described above except the antagonist and the other (C2) contains C1 plus a 1000-fold excess of unlabelled PAF, were also prepared and incubated simultaneously with the test samples. After 1 hour incubation, each solution was filtered rapidly under *vacuo* through a WHATMAN GF/C glass fibre filter in order to separate unbound PAF from bound PAF. (The word WHATMAN is a trade mark.) The residue in each case was rapidly washed 4 times with 5 ml cold (4°C) Tris-buffer solution. Each washed residue was dried under vacuum on a sampling manifold and placed into vials containing 20 ml of OPTIPHASE MP scintillation fluid and the radioactivity counted in a liquid scintillation counter. (The word OPTIPHASE is a trade mark.) Defining the counts for total binding with antagonist from a test sample as "TBA"; the counts for total binding from the control sample C1 as "TB"; and the counts for nonspecific binding from the control sample C2 as "NSB"; the percent inhibition of each test antagonist can be determined by the following equation:

%Inhibition = [(TB-TBA)/SB]x100
where the specific binding SB = TB-NSB

Table 1: Result for inhibition of [^{3}H]-PAF receptor binding

Example	Inhibition of [^{3}H]-PAF binding IC_{50} nM
2	10

PHARMACOLOGY EXAMPLE 2

The activity of the compounds of general formula I is also demonstrated *in vivo* by their ability to reverse the hypotension caused by an infusion of PAF in rats. Male Sprague-Dawley rats (300-350 g) were anaesthetised with a mixture of sodium pentobarbitone, 22.5 mg/kg and thiopental 62.5 mg/kg. Through a midline incision in the neck, the trachea was cannulated and the animals breathed spontaneously. A carotid artery was cannulated for the measurement of blood pressure and this signal was used to trigger a rate meter to measure heart rate. Both jugular veins were cannulated: one for the infusion of PAF and the other for the bolus administration of test compounds.

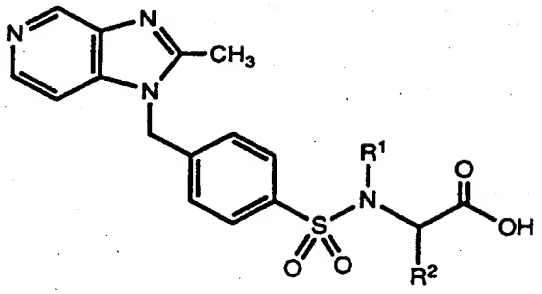
PAF, 100 ng/kg/min was infused *i.v.* until a sustained fall in mean blood pressure of 50 mmHg was achieved. Test compounds were administered *i.v.* as a bolus and resulted in a dose dependent reversal of the PAF induced hypotension. The peak of this reversal was measured and the dose to cause a 50% reversal of the hypotensive PAF response (ED_{50}) calculated by straight line interpolation and the results are presented in Table 2.

Table 2: Result (average of several tests) for inhibition of PAF-induced hypotension in the rat

Example	ED_{50} (μg/kg *i.v.*)
2	32

CLAIMS

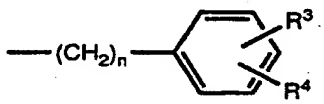
1. A compound of formula (II):



(II)

wherein

R1 represents hydrogen, -C_1-C_6 alkyl, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, -COC_1-C_6 alkyl, -CO_2C_1-C_6 alkyl, -(COC_1-C_6 alkyl)phenyl, - (CO_2C_1-C_6 alkyl)phenyl, -(C_1-C_6 alkyl)OC_1-C_6 alkyl, -(C_1-C_6 alkyl)SC_1-C_6 alkyl, -(C_1-C_6 alkyl)CO_2C_1-C_6 alkyl, -C_3-C_8 cycloalkyl, -C_4-C_8 cycloalkenyl or a group -D wherein D represents a group:



wherein n is an integer from 0 to 3, and each of R3 and R4 is independently hydrogen, -C_1-C_6 alkyl, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, halogen, -CN, -CO_2H, -CO_2C_1-C_6 alkyl, -$CONH_2$, -$CONHC_1$-C_6 alkyl, -$CONH(C_1$-C_6 alkyl$)_2$, -CHO, -CH_2OH, -CF_3, -OC_1-C_6 alkyl, - SC_1-C_6 alkyl, -SOC_1-C_6 alkyl, -SO_2C_1-C_6 alkyl, -NH_2 or -NHCOMe;

R2 represents hydrogen, halogen, -C_1-C_6 alkyl optionally substituted by one or more halogen atoms, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, -(C_1-C_6 alkyl)CO_2C_1-C_6 alkyl, -(C_1-C_6 alkyl)SC_1-C_6 alkyl, -(C_1-C_6 alkyl)OC_1-C_6 alkyl, -(C_1-C_6

alkyl)N(C_1-C_6 alkyl)$_2$, -C_3-C_8 cycloalkyl, -C_4-C_8 cycloalkenyl, -(C_1-C_6 alkyl)C_3-C_8 cycloalkyl, - (C_1-C_6 alkyl)C_4-C_8 cycloalkenyl, -(C_1-C_6 alkyl)OC_3-C_8 cycloalkyl, -(C_1-C_6 alkyl)OC_4-C_8 cycloalkenyl, -(C_1-C_6 alkyl)SC_3-C_8 cycloalkyl, -(C_1-C_6 alkyl)SC_4-C_8 cycloalkenyl, a side chain of a naturally occurring amino acid, a group -D as defined above or a -(C_1-C_6 alkyl)OD group wherein D is as defined above;

or a pharmaceutically or veterinarily acceptable salt thereof, for use in human or veterinary medicine.

2. The use of a compound of formula (II) or salt thereof as defined in claim 1 in the preparation of a pharmaceutical composition adapted for oral, topical, rectal or parenteral administration or for inhalation for the management of diseases or conditions mediated by PAF.

3. A pharmaceutical composition in dosage unit form, for the management of diseases or conditions mediated by PAF, comprising a compound of formula (II) or salt thereof as defined in claim 1, and one or more pharmaceutically acceptable carriers.

4. A method for the management of diseases or conditions mediated by PAF, comprising administering to the patient an effective amount of a compound of formula (II) or salt thereof as defined in claim 1.

5. A use as claimed in claim 1 or claim 2, a composition as claimed in claim 3, or a method as claimed in claim 4, for the management of inflammatory disorders; such as rheumatoid arthritis, osteoarthritis and eye inflammation, cardiovascular disorder, thrombocytopenia, asthma, endotoxin shock, adult respiratory distress syndrome, glomerulonephritis, immune regulation, gastric ulceration, transplant rejection, psoriasis, allergic dermatitis, urticaria, multiple sclerosis, cerebral, myocardial and renal ischemia.

6. A use as claimed in claim 1 or claim 2, a composition as claimed in claim 3, or

a method as claimed in claim 4, wherein the compound of formula (II) used is one in which R^1 represents a hydrogen atom, a -C_1-C_6 alkyl group, a -C_2-C_6 alkenyl group or a group -D as defined in claim 1.

7. A use as claimed in claim 1or claim 2, a composition as claimed in claim 3, or a method as claimed in claim 4, wherein the compound of formula (II) used is one in which R^2 represents a hydrogen atom, a -C_1-C_6 alkyl group, a -C_2-C_6 alkenyl group, a -(C_1-C_6 alkyl)C_3-C_8 cycloalkyl group, a side chain of a naturally occurring amino acid or a group D as defined in claim 1.

8. A use as claimed in claim 1 or claim 2, a composition as claimed in claim 3, or a method as claimed in claim 4, wherein the compound of formula (II) used is one containing a group D as defined in claim 1 wherein R^3 represents a hydrogen atom, a - C_1-C_6 alkyl group, a halogen atom, a -CF_3 group or a -OC_1-C_6 alkyl group, and R^4 represents a hydrogen atom or a -OC_1-C_6 alkyl group.

9. A use as claimed in claim 1 or claim 2, a composition as claimed in claim 3, or a method as claimed in claim 4, wherein the compound of formula (II) used is N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucine, or a pharmaceutically acceptable salt thereof.

10. A use as claimed in claim 1 or claim 2, a composition as claimed in claim 3, or a method as claimed in claim 4, wherein the compound of formula (II) used is selected from:

N-4-(1H-2-Methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucine,
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-D-leucine,
N-Ethyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucine,
N-Allyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucine,
N-Propyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucine,
N-Benzyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucine,
N-4-Methoxybenzyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl) phenyl-

sulphonyl-L-leucine,
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-isoleucine,
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-phenylalanine,
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-valine,
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-tryptophanol,
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-methionine,
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-O-methyl-L-tyrosine,
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-norleucine,
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-phenylglycine,
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-t-butylglycine,
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-D,L-ethylglycine,
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-D,L-allylglycine,
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-t-butylalanine,
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-cyclopropylalanine,
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-cyclopentylalanine,
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-cyclohexylalanine,

and their pharmaceutically or veterinarily acceptable salts.

INTERNATIONAL SEARCH REPORT

Internat Application No
PCT/GB 94/02460

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/415

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,92 03423 (BRITISH BIOTECHNOLOGY LTD) 5 March 1992 cited in the application	

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 February 1995	15.03.95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Klaver, T

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Interna: l Application No
PCT/GB 94/02460

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